Data Evaluation Report on the Abiotic Hydrolysis of Fenamidone

PMRA Submission Number USEPA MRID Number 45385829

Data Requirement:: PMRA Data Code:
EPA DP Barcode: D275213
OECD Data Point:
EPA Guideline: 161-1

Test material:
Chemical name

IUPAC: (+)-(4*S*)-4-Methyl-2-methylthio-4-phenyl-(1H)-1-phenylamino-2-imidazolin-5-one.

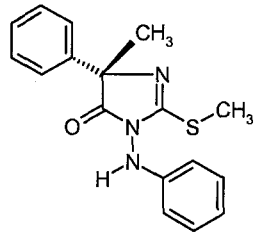
CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (*S*)-.

CAS No: 161326-34-7.

Synonyms: Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydro-4H-imidazol-4-one.
(*S*)-1-Anilino-4-methyl-2-methylthio-4-phenylimidazolin-5-one.
(*S*)-5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one.
Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (5*S*)-.
(5*S*)-3,5-Dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-4*H*-imidazol-4-one.
RPA407213.

SMILES string:

Chemical Structure:



Primary Reviewer: Dana Worcester
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Date: 26 August, 2002

Company Code: [for PMRA]

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Date:

Company Code: [for PMRA]
Active Code: [for PMRA]
Use Site Category: [for PMRA]
EPA PC Code: 046679

CITATION: Corgier, M. M., and G. P. Turier. 1998. 14C-RPA407213. Hydrolysis at pH 4, 5, 7 and 9, at 25°C. Unpublished study performed by Rhône-Poulenc Agro, Centre de Rescherche de la Dargoire, Lyon France and sponsored by Aventis CropScience, Research Triangle Park, NC. Study Number 96-108; Report Reference: R&D/CRLD/AN/9716604. The study was initiated on October 16, 1996, and completed on April 8, 1998.

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Aventis's response to EFED's review of the Reduced Risk Document performed on October 12, 2001. No MRID

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PMRA

Submission Number {.....} EPA MRID Number 45385829

Regulatory Conclusions:
This study can be used to fulfill the hydrolysis data requirement (§161-1).

Kinetics and Transformation Products:

	Half-life (Days)	Major transformation products
pH 4	41.8	4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione (RPA405862/RPA410193)
pH 5	223.6	None
pH 7	407.7	None
pH 9	27.6	(R,S)-2-methyl-2-phenyl-N-(phenylazocabonyl)glycine (RPA409344) 4-methyl-2-methylthio-4-phenyl-2-imidazolin-5-one (RPA408056)

Note: "RPA 405862" was originally used to refer to the racemic mixture. However, the studies were actually conducted with the *S*- enantiomer (RPA 410193), which is the pesticide active enantiomer. Aventis's response to USEPA's review of the Reduced Risk Document.

EXECUTIVE SUMMARY

The hydrolysis of [C-phenyl-U-^{14}C]-labeled (+)-(4*S*)-4-methyl-2-methylthio-4-phenyl-(1H)-1-phenylamino-2-imidazolin-5-one (fenamidone, RPA407213), at 3.9 mg a.i./L, was studied in the dark at 25 ± 1°C in sterile aqueous buffered solutions at pH 4 (citrate), pH 5 (citrate), pH 7 (phosphate), and pH 9 (borate) for 31 days. This study was conducted in accordance with USEPA Subdivision N Guideline §161-1 and in compliance with the U.S. EPA GLP standards (40 CFR Part 160, 1989). The test system consisted of glass flasks sealed with screw caps and maintained in a dark temperature-controlled incubator. Volatiles were not trapped in the kinetics experiment but were addressed in a supplementary experiment. Duplicate samples of each treated buffer solution were collected and analyzed at 0, 5, 10, 14, 19, 25, and 31 days

posttreatment. The samples were analyzed directly without modification using LSC and HPLC. HPLC peaks were identified by comparison to reference standards. Identifications were confirmed using LC/MS.

Total [^{14}C]residue recovery ranged from 99.5 to 102.3% of the applied in the pH 4 buffer, 98.4 to 101.3% in the pH 5 buffer, 96.2 to 101.4% in the pH 7 buffer, and 99.4 to 101.7% in the pH 9 buffer. There was no pattern of decline.

In the pH 4 buffer, [^{14}C]fenamidone decreased from 100.00% of the applied at day 0 to 59.66% at 31 days posttreatment (final sampling interval). The major transformation product was RPA405862/RPA410193 (4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione), with a maximum concentration of 38.76% of applied at 31 days posttreatment. Hydrolate C (unidentified) was isolated at a maximum 0.15% of the applied at 31 days. Other unidentified radioactivity totaled a maximum of 2.84% of the applied at 19 days. Volatiles were not measured in the kinetics experiment.

In the pH 5 buffer, [^{14}C]fenamidone decreased from 100.00 ± 0.0% of the applied at day 0 to 91.15 ± 0.1% at 31 days posttreatment. No major degradation products were identified. RPA405862/RPA410193 was a maximum of 6.87% of the applied at 31 days posttreatment. Hydrolyte C was ≤0.17% at all sampling intervals. Other unidentified radioactivity totaled ≤0.44% of the applied at all sampling intervals.

In the pH 7 buffer, [^{14}C]fenamidone decreased from 100.00 ± 0.0% of the applied at day 0 to 95.34 ± 0.5% at 31 days posttreatment. No major degradation products were identified. RPA409344 [(R,S)-2-methyl-2-phenyl-N-(phenylazocabonyl)glycine] was a maximum of 2.88% of the applied at 31 days. RPA408056 (4-methyl-2-methylthio-4-phenyl-2-imidazolin-5-one) was a maximum 0.98% of the applied at 31 days. Hydrolyte C was ≤0.72% at all sampling intervals. Other unidentified radioactivity totaled ≤0.05% of the applied at all sampling intervals.

In the pH 9 buffer, [^{14}C]fenamidone decreased from 100.00 ± 0.0% of the applied at day 0 to 47.10 ± 0.7% at 31 days posttreatment. The major transformation products were RPA409344 and RPA408056, with maximum concentrations of 32.16 ± 0.2 and 10.09 ± 0.1% of applied at 31 days. Hydrolytes C and E were ≤1.23% and ≤4.57% of the applied, respectively. Other unidentified radioactivity totaled ≤2.12% of the applied at all sampling intervals.

In a supplementary experiment, volatiles were not detected in the headspace of treated pH 4, 5, 7, or 9 buffer solutions that were incubated in the dark at 24-25°C for 31 days.

A transformation pathway was proposed by the study author. Fenamidone degrades directly to RPA405862/RPA410193, RPA409344, RPA408056, and methyl mercaptan (CH_3SH). In an acidic solution, the major degradate is RPA405862/RPA410193 with the formation of methyl mercaptan. In a basic solution, the predominant degradate is RPA409344 with the formation of methyl mercaptan. RPA408056 is also a significant degradate under the basic conditions found in this study.

The half-lives (DT50) of fenamidone, assuming pseudo-first order kinetics, were:

41.8 days (r^2 = 0.9908) at pH 4;
223.6 days (r^2 = 0.9805) at pH 5;
407.7 days (r^2 = 0.9257) at pH 7; and
27.6 days (r^2 = 0.9899) at pH 9.

This study is classified acceptable and satisfies the guideline requirement for a hydrolysis study in sterile buffer solutions (§161-1).

RESULTS SYNOPSIS:

	Half-life (Days)	Major transformation products
pH 4	41.8	4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione (RPA405862/RPA410193)
pH 5	223.6	None
pH 7	407.7	None
pH 9	27.6	(R,S)-2-methyl-2-phenyl-N-(phenylazocabonyl)glycine (RPA409344) 4-methyl-2-methylthio-4-phenyl-2-imidazolin-5-one (RPA408056)

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: This study was conducted in accordance with USEPA Subdivision N Guideline §161-1 and E.U. Guideline C7. No significant deviations from the Subdivision N guideline was noted.

COMPLIANCE: This study was conducted in compliance with USEPA GLP Standards (40 CFR Part 160) and OECD GLP in the Testing of Chemicals (Paris, 1998; p. 3). Signed and dated Data Confidentiality, GLP, and Quality Assurance statements were provided (pp. 2-4).

A. MATERIALS:

1. Test Material [C-phenyl-U-^{14}C]RPA 407213

Chemical Structure:

Description: Not provided.

Purity: Radiochemical purity: >98% (pp. 11, A1-A5)
Lot/Batch No. CFQ 9085
Analytical purity: Not provided.
Specific activity: 38 mCi/mM (1.41 GBq/mM)
Location of the label: Uniformly labeled on the phenyl ring.

99.8% *S*-enantiomer

Storage conditions of test chemicals: Not specified.

Physico-chemical properties of fenamidone.

Parameter	Details	Comments
Solubility:	7.8 mg/L in water at 20°C. 86.1 g/L in acetonitrile at 20°C.	
Vapor pressure/volatility:	Not reported.	
UV absorption:	230 nm	In acetonitrile:water (55:45, v:v).
pK_a:	Not reported.	
K_{ow}	Not reported.	
Stability at room temperature:	Not reported.	

Data obtained from pp. 11, 43 in the study report.

2. Buffer Solution: Buffer solutions were made as follows:

Table 1: Description of buffer solutions.

pH	Type of buffer and final molarity	Composition
4	0.02 M citrate	4.20 g of citric acid monohydrate was dissolved in 950 mL water, adjusted to pH 4 with 1 N NaOH, then brought to final volume of 1000 mL with water.
5	0.02 M citrate	4.20 g of citric acid was dissolved in 950 mL water, adjusted to pH 5 with 1 N NaOH, then brought to final volume of 1000 mL with water.
7	0.02 M phosphate	2.70 g of KH_2PO_4 was dissolved in 900 mL water, adjusted to pH 7 with 1 N NaOH, then brought to final volume of 1000 mL with water.
9	0.02 M borate	2.47 g of boric acid was dissolved in 1900 mL of water, adusted to pH 9 with 1 N NaOH, then brought to final volume of 2000 mL with water.

Data obtained from pp 12-13 in the study report.

B. EXPERIMENTAL CONDITIONS

1. Preliminary Study: A preliminary study was not conducted.

2. Experimental condition Table 2: Experimental parameters.

Parameters		Details
Duration of the study		31 days for all treatments
Test concentrations (mg a.i./L) Nominal: Measured:		 3.89 mg/L (p. 14) 3.9 mg/L (p. 18)
No. of replications		2
Preparation of test medium	Volume used/treatment	20 mL
	Method of sterilization	Prior to use, all glassware and the buffer solutions were autoclave-sterilized at 121°C for 35 minutes.
	Co-solvent (type/concentration)	Acetonitrile, 1% by volume (0.2 mL added to 19.8 mL of buffer solution)
Test apparatus (type/material/volume)		24 mL glass flasks fitted with screw caps.
Details of traps for volatile, if any		Volatiles were not trapped in the kinetics experiment. Volatilization was addressed in a supplementary study.
If no traps were used, is the test system closed/open?		Closed.
Is there any indication of the test material adsorbing to the walls of the test apparatus?		Not indicated.
Experimental conditions Temperature (°C) Lighting		 25 ± 1°C; monitored hourly. Dark.
Other details, if any		None.

Data obtained from pp. 13-15 in the study report unless noted otherwise.

3. Supplementary Experiments: In order to address volatilization, duplicate bottles of each buffer solution (100 mL/sample) were treated as described and incubated in the dark at 25 ± 1°C for 35 days. Then the bottles were attached to a volatile trapping apparatus consisting of one tube (75 mL) of ethyleneglycol monomethyl ether (EGME), two tubes (75 mL each) of ~2N NaOH, and one tube (75 mL) of water. The headspace air was pumped through the trapping solutions for 30 minutes. Aliquots of the trapping solutions were then analyzed for total radioactivity using LSC.

In order to confirm the sterility of the test solutions, aliquots (25 µL) of the 31-day pH 4, 5, 7, and 9 buffer solutions were applied to screw-capped bottles (60-mL) containing autoclave-sterilized (121°C for 35 minutes) nutrient solution (pH 7.2) consisting of 0.01 mg/L D(+) glucose, 0.005 mg/L yeast extract and 0.005 mg/L Bacto-peptone (p. 16). The treated nutrient solutions were incubated 3 days with orbital stirring at 27°C. Following incubation, the solutions were assessed visually (clear/cloudy) and optical density was determined by measuring absorbance at 500 nm.

To establish the stability of fenamidone, duplicate aliquots of the 31-day buffer solutions were re-analyzed by HPLC as described below after approximately 6 months of frozen storage (ca. -20°C; Table 11, p. 39).

4. Sampling:

Table 3: Sampling details.

Criteria	Details
Sampling intervals	0, 5, 10, 14, 19, 25 and 31 days for all treatments.
Sampling method	Two flasks of each buffer solution were collected at each sampling interval.
Sampling methods for the volatile compounds, if any	Volatiles were not collected in the definitive study.
Sampling intervals/times for: pH measurement Sterility check	 Each sampling interval. Final sampling interval.
Sample storage before analysis	Analyses were generally performed on the day of sampling (p. 17). If not, samples were stored frozen at approximately -20°C.
Other observation, if any:	None

Data obtained from p. 15 unless noted otherwise.

C. ANALYTICAL METHODS

Extraction/clean up/concentration methods, if used: Samples were analyzed as collected, without manipulation or modification.

Volatile residue determination: Volatiles were not trapped in the kinetics experiment.

Total ^{14}C measurement: Total ^{14}C was analyzed by LSC.

Derivatization method, if used: A derivatization method was not employed.

Identification and quantification of parent compound: Identification and quantification of fenamidone was performed by reverse-phase HPLC using the following operating conditions: Alltima C-18 column (250 x 4.6 mm, 5 µm) column at ambient temperature; an isocratic mobile phase of acetonitrile:water:trifluoroacetic acid (45:55:0.1:, v:v:v); a flow rate of 1 mL/minute; an injection volume of 50 µL; and UV (230 nm) and radioactive flow detection (p. 17). Femamidone was identified by comparison to cochromatographed reference standards; the retention time using this HPLC system was 21.57-21.60 minutes (Table XII, p. 40). Identification was confirmed by LC/MS using a Triple Quadripole MS equipped with an Atmospheric Pressure Ionization interface (p. 94).

Identification and quantification of transformation products: Transformation products were isolated and quantified by HPLC as described for the parent compound and identified by

comparison to reference standards. Retention times using this HPLC system were 7.98-8.20 minutes for RPA 405862/RPA410193; 9.95-10.00 minutes for RPA409344; and 3.37-3.38 minutes for RPA408056 (Table XII, p. 40). Identification of RPA408056, RPA405862, and RPA 409344 was confirmed using LS/MS as described (p. 94).

Detection limits (LOD, LOQ) for the parent compound: The HPLC system was capable of detecting and evaluating a peak equivalent to 1.22% of the radioactivity injected or 24 ng (expressed as parent compound; p. 19).

Detection limits (LOD, LOQ) for the transformation products: The sensitivity of the HPLC system was the same as for the parent compound.

II. RESULTS AND DISCUSSION

A. TEST CONDITIONS: During the study, the pH of the pH 4 buffer solutions ranged from 4.15-4.21, of the pH 5 buffer solutions ranged from 5.09-5.16, of the pH 7 buffer solutions ranged from 7.06-7.15, and of the pH 9 buffer solutions ranged from 8.83-9.08 (Table II, p. 30). Mean temperature ranged from 24.8-25.0°C (Table 1, p. 29). The sterility of the samples was confirmed at the final sampling interval (Table III, p. 31).

B. MASS BALANCE: Total [^{14}C]residue recovery ranged from 99.5 to 102.3% of the applied at pH 4, 98.4 to 101.3% at pH 5, 96.2 to 101.4% at pH 7, and 99.4 to 101.7% at pH 9 (Tables V and VI, pp. 33-34).

Table 4: Hydrolysis of [^{14}C]fenamidone, expressed as the percentage of the applied radioactivity (n = 2, mean ± s.d.), at pH 4.*

Compound		Sampling times (days)						
		0	5	10	14	19	25	31
Fenamidone (RPA407213)		100.00 ± 0.0	91.61± 0.1	84.60 ± 0.1	80.06 ± 0.4	70.44 ± 1.9	66.81 ± 0.4	59.66 ± 0.2
RPA405862/RPA410193 (Hydrolate A)		0.00 ± 0.0	8.39 ± 0.1	15.40 ± 0.1	19.95 ± 0.5	25.63 ± 1.0	33.20 ± 0.4	38.76 ± 0.1
RPA409344 (Hydrolate B)		0.00	0.00	0.00	0.00	0.61	0.00	0.19
RPA408056 (Hydrolate D)		0.00	0.00	0.00	0.00	0.49	0.00	0.87
Hydrolate C		0.00	0.00	0.00	0.00	0.00	0.00	0.15
Others		0.00	0.00	0.00	0.00	2.84	0.00	0.37
Volatiles	CO_2	Volatiles were not measured in the kinetics study.						
	Organic							
Total % recovery		101.2 ± 0.5	101.6 ± 0.0	101.9 ± 2.2	100.9 ± 1.6	100.3 ± 0.2	102.3 ± 0.3	99.5 ± 0.1

* Mean and s.d. values were calculated by the reviewer using Excel with data from Table V, p. 33, and Table VII, p. 35, of the study report

.Table 5: Hydrolysis of [^{14}C]fenamidone, expressed as the percentage of the applied radioactivity (n = 2, mean ± s.d.), at pH 5.*

Compound		Sampling times (days)						
		0	**5**	**10**	**14**	**19**	**25**	**31**
Fenamidone (RPA407213)		100.0 ± 0.0	98.29 ± 0.1	97.39 ± 0.2	96.43 ± 0.1	93.69 ± 0.1	92.21 ± 0.1	91.15 ± 0.1
RPA405862/RPA410193 (Hydrolate A)		0.00	1.71	2.61	3.39	4.40	5.65	6.87
RPA409344 (Hydrolate B)		0.00	0.00	0.00	0.00	0.78	0.83	1.14
RPA408056 (Hydrolate D)		0.00	0.00	0.00	0.19	0.84	0.70	0.49
Hydrolate C		0.00	0.00	0.00	0.00	0.00	0.17	0.00
Others		0.00	0.00	0.00	0.00	0.30	0.44	0.11
Volatiles	CO_2	Volatiles were not measured in the kinetics study, but in a separate study it was demonstrated that volatilization did not occur under the experimental conditions of the study.						
	Organic							
Total % recovery		98.7 ± 2.0	99.9 ± 0.7	98.9 ± 1.6	100.4 ± 1.7	101.3 ± 0.5	101.0 ± 0.6	98.4 ± 0.1

* Mean and s.d. values were calculated by the reviewer using Excel with data from Table V, p. 33, and Table VIII, p. 36, of the study report.

Table 6: Hydrolysis of [^{14}C]fenamidone, expressed as the percentage of the applied radioactivity (n = 2, mean ± s.d.),
at pH 7.[1]

Compound		Sampling times (days)						
		0	**5**	**10**	**14**	**19**	**25**	**31**
Fendamidone (RPA407213)		100.0 ± 0.0	100.0 ± 0.0	98.06 ± 0.3	98.35 ± 0.6	96.54 ± 0.3	96.02 ± 0.0	95.34 ± 0.5
RPA405862/RPA410193 (Hydrolate A)		0.00	0.00	0.11	0.00	0.45	0.52	0.81
RPA409344 (Hydrolate B)		0.00	0.00	1.12	1.26	2.10	2.50	2.88
RPA408056 (Hydrolate D)		0.00	0.00	0.00	0.40	0.91	0.91	0.98
Hydrolate C		0.00	0.00	0.72	0.00	0.00	0.00	0.00
Others		0.00	0.00	0.00	0.00	0.00	0.05	0.00
Volatiles	CO_2	Volatiles were not measured in the kinetics study.						
	Organic							
Total % recovery		98.5*	99.3 ± 0.6	100.3 ± 2.4	99.1 ± 0.8	97.9 ± 0.9	101.4 ± 0.1	96.2 ± 3.6

1 Mean and s.d. values were calculated by the reviewer using Excel with data from Table VI, p. 34, and Table IX, p. 37, of the study report.

* The study author reported that one value was used due to the other value being an outlier and not homogenous with other values.

Table 7: Hydrolysis of [^{14}C]fenamidone, expressed as the percentage of the applied radioactivity (n = 2, mean ± s.d.), at pH 9.*

Compound		Sampling times (days)						
		0	5	10	14	19	25	31
Fenamidone (RPA407213)		100.0 ± 0.0	95.40 ± 0.2	82.23 ± 1.2	73.31 ± 0.2	66.30 ± 1.6	55.56 ± 0.3	47.10 ± 0.7
RPA405862/RPA410193 (Hydrolate A)		0.00	0.00	1.19	1.71	2.19	3.11	3.76
RPA409344 (Hydrolate B)		0.00 ± 0.0	4.61 ± 0.2	12.07 ± 0.1	17.39 ± 0.5	23.92 ± 0.6	28.48 ± 1.2	32.16 ± 0.2
RPA408056 (Hydrolate D)		0.00 ± 0.0	0.00 ± 0.0	3.29 ± 0.6	4.59 ± 0.1	5.87 ± 0.1	7.87 ± 1.1	10.09 ± 0.1
Hydrolate C		0.00	0.00	1.23	1.07	0.00	0.89	0.22
Hydrolate E		0.00	0.00	0.00	0.70	1.26	3.38	4.57
Others		0.00	0.00	0.00	1.23	0.47	0.72	2.12
Volatiles	CO_2	Volatiles were not measured in the kinetics study.						
	Organic							
Total % recovery		100.9 ± 0.6	101.7 ± 1.1	100.2 ± 0.8	100.5 ± 0.1	99.4 ± 0.1	101.2 ± 0.6	100.6 ± 0.3

* Mean and s.d. values were calculated by the reviewer using Excel with data from Table VI, p. 34, and Table X, p. 38, of the study report.

C. TRANSFORMATION OF PARENT COMPOUND: In the pH 4 buffer solution, fenamidone decreased from 100.00% of the applied at day 0 to 59.66% at 31 days (final sampling interval; Table VII, p. 35).

In the pH 5 buffer solution, fenamidone decreased from 100.00% of the applied at day 0 to 91.15% at 31 days (Table VIII, p. 36).

In the pH 7 buffer solution, fenamidone decreased from 100.00% of the applied at day 0 to 95.34% at 31 days (Table IX, p. 37).

In the pH 9 buffer solution, fenamidone decreased from 100.00% of the applied at day 0 to 47.10% at 31 days (Table X, p. 38).

HALF-LIFE: The half-lives for fenamidone in the pH 4, 5, 7, and 9 buffer solutions were determined by the reviewer using linear regression analysis based on pseudo-first order kinetics as calculated by Excel 2000. Respective values were determined to be 41.8, 223.6, 407.7, and 27.6 days. These values are very similar to those reported by the study author, who used Excel v. 7 software (p. 21).

Half-lives*

pH	First order linear			DT50* (days)	DT90 (days)
	Half-life (day)	Regression equation	r^2		
4	41.8	Linear form y = mx + b as lnC= -kt + lnC_0; lnC_0 is initial concentration (b = y intercept), lnC is concentration at time t (y), k is the slope (m), t is time (x) or kt = lnC_0 - lnC. Half-life (t ½) = -(ln 2/k).	0.9908	41.8	ND
5	223.6		0.9805	223.6	ND
7	407.7		0.9257	407.7	ND
9	27.6		0.9899	27.6	ND

*Half-lives calculated by reviewer using data obtained from pp. 35-38 of study report. Values identified as DT50s by the study author are in fact half-lives calculated, as a the reaction followed first order kinetics.
ND Not determined.

TRANSFORMATION PRODUCTS: In the pH 4 buffer solution, the major transformation product was identified as RPA405862/RPA410193 [4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione and its enantiomer (*S*)-4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione; Hydrolyte A; Table VII, p. 35]. The maximum concentration was 38.76% of the applied at 31 days posttreatment (final sampling interval. RPA409344 [Hydrolyte B; (R,S)-2-methyl-2-phenyl-N-(phenylazocabonyl)glycine *or* (R,S)-2-phenyl-2-(phenylazocarbonylamino)propionic acid] and RPA408056 (Hydrolyte D; 4-methyl-2-methylthio-4-phenyl-2-imidazolin-5-one) were each <1% of the applied at all sampling intervals. Hydrolyte C (not identified, Rt 2.95 minutes), detected only at 31 days posttreatment, was 0.15% of the applied. "Others" (not defined) was a maximum 2.84% of the applied at 19 days.

In the pH 5 buffer solution, no major degradation products were identified. RPA405862/RPA410193 was a maximum of 6.87% of the applied at 31 days. Hydrolyte C was ≤0.17% at all sampling intervals. "Others" were ≤0.44% at all sampling intervals.

In the pH 7 buffer solution, no major degradation products were identified. RPA409344 was a maximum of 2.88% of the applied at 31 days. Hydrolyte C was ≤0.72% at all sampling intervals. "Others" were ≤0.05% at all sampling intervals.

In the pH 9 buffer solution, the major transformation products detected were RPA409344 at a maximum 32.16% of the applied at 31 days posttreatment and RPA408056 at a maximum 10.09% at 31 days. The minor transformation products were RPA405862/RPA410193 at a maximum of 3.76% of the applied at 31 days. Hydrolyte C was ≤1.23% at all sampling intervals. Hydrolyte E was ≤4.57% at all sampling intervals. Also, on the HPLC chromatograms for pH 9 at 14 and 31 days, there is a Hydrolate G at approximately Rt 2.03 that is not included in the data tables (pp. 62, 63). "Others" were ≤2.12% at all sampling intervals.

VOLATILIZATION: Volatiles were not measured in the kinetics experiment. In a supplementary study, it was demonstrated that volatilization did not occur under the conditions used in this study.

PATHWAYS: A transformation pathway was proposed by the study author (p. 22). Fenamidone degrades directly to RPA405862/RPA410193, RPA409344, RPA408056, and methyl mercaptan

(CH_3SH). In an acidic solution, the major degradate is RPA405862/RPA410193 with the formation of methyl mercaptan. In a basic solution, the predominant degradate is RPA409344 with the formation of methyl mercaptan. RPA408056 is also a significant degradate under the basic conditions found in this study.

Table 8: Chemical names for identified transformation products of fenamidone

Applicant's Code Name	CAS Number	Chemical Names	Chemical formula	Molecular weight (g/mol)	Smiles string
RPA408056		IUPAC: 4-Methyl-2-methylthio-4-phenyl-2-imidazolin-5-one IUPAC: 5-Methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one CAS: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-		220.3	
RPA405862	161326-62-1	IUPAC: 4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione IUPAC: 5-Methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione CAS: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-3-(phenylamino)-		281.3	
RPA410193 (fungicide active enantiomer)	**161326-34-7**	IUPAC: (*S*)-4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione; *S*-enantiomer of RPA405862		281.3	
RPA409344		IUPAC: (*R,S*)-2-methyl-2-phenyl-N-(phenylazocarbonyl)glycine *or* (R,S)-2-phenyl-2-(phenylazocarbonylamino)propionic acid IUPAC: (*R,S*)-2-phenyl-2-(phenylazocarbonylamino)propionic acid		297.3	

D. SUPPLEMENTARY EXPERIMENT-RESULTS

No volatile [^{14}C]compounds (reported as 0.00% of the applied) were found in the headspace air from bottles of treated buffer solutions that were incubated for 35 days (Table IV, p. 32). The ethyleneglycol monomethyl ether, 2N NaOH, and water solutions (75 mL/tube) each measured at ≤1560 dpm.

The treated buffer solutions sampled at 31 days posttreatment were shown to have an optical density similar to the sterilized untreated buffer solutions (Table III, p. 31). The treated solutions were judged to have remained sterile during the study.

Fenamidone was stable during 6 months of frozen storage in the pH 4, 5, and 7 buffer solutions (Table XI, p. 39). The concentrations of fenamidone in the reanalyzed samples were within 2%

of the applied at pH 4 and were higher at pH 5 and 7. The concentration of Hydrolyte A was similar to or higher in the reanalyzed samples; other hydrolytes were generally present in the original samples at ≤1.16% of the applied and were not detected in the reanalysis. Some slight degradation may have occurred in the pH 9 buffer solution, since fenamidone decreased by 4.5% of the applied (from 47.57 to 43.05%) and the four hydrolytes and "Others" each increased by about 1%.

III. STUDY DEFICIENCIES: No deficiencies were identified. This study can be used to fulfill the hydrolysis data requirement (§161-1).

IV. REVIEWER'S COMMENTS:

1. In the document *Reduced Risk Rationale for the Use of Fenamidone on Potatoes and Vegetables* (B0003264, no MRID), it is reported that fenamidone is the S-enantiomer compound with none of the R-enantiomer present (p. 16). It is further stated that analysis demonstrated that all of the metabolites of fenamidone that retain the imidazolinone ring are also pure S-enantiomers. No evidence was provided to support this statement. The registrant notes that the racemic mixture was often referenced in the original study reports.

   Therefore, although the study author identified Hydrolyte A as being a mixture of RPA405862 (4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione) and RPA410193 [(S)-4-methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione], Photolyte A in fact consists only of RPA410193. To remain consistent with the study report, the term RPA405862/RPA410193 is used throughout this DER.

2. The registrant's code numbers used in this MRID do not match the code numbers presented in the *Reduced Risk Rationale for the Use of Fenamidone on Potatoes and Vegetables* (B0003264, no MRID). For example, RPA405862/RPA410193 is RPA410193, RPA409344 is RPA413350, and RPA408056 is RPA412708. The reason for the different code numbers was not discussed. Using the conversion of RPA405862/RPA410193 to RPA410193 and the chemical names provided with the studies as a guide, it appears that in the studies, the registrant's code numbers are for the *R*-enantiomer form or the racemic mixture. In the Reduced Risk petition, the registrant states that only the *S*-enantiomer form of the parent and transformation products exist. In the response to the USEPA's comments to the review of the Reduced Risk Document, states that only the codes for the *S*-enantiomer were used for simplicity

3. Multiple IUPAC names were found for fenamidone and several of its transformation products. It could not be determined which name was currently preferred. All of the chemicals names that were used in the MRIDs in this data package are included in the *Chemical names for identified transformation products* table in this DER and with the attached chemical structures.

4. Several minor peaks identified on the HPLC chromatogram at <5% of the applied were not addressed by the study author. These peaks were identified in the data tables as

"Hydrolytes", but no evidence was provided that the individual peaks represented single compounds. These peaks are not discussed in the text. Hydrolates C and E (Rt approximately 2.95 and 2.32-2.45 minutes, respectively) were quantified but were not identified. Hydrolate G appears on the HPLC chromatograms for the 14 and 31 day pH 9 butter solutions (Figures B9 and B10, pp. 62 and 63), but is not included in the data tables.

5. The data tables include entries for radioactive residues decribed as "Others". The study author does not define or discuss "Others". It could not be determined if "Others" represents radioactivity that was not associated with a discrete HPLC peak or radioactivity that was associated with peaks other than the 5-6 peaks the study author chose to include in the data tables.

6. Methyl mercaptan was identified as a degradation product in the transformation pathway proposed by the study author. The samples were not analyzed for methyl mercaptan. No evidence is provided that methyl mercaptan is a degradate of fenamidone. In the response to the USEPA's review of the Reduced Risk Document, Aventis clarified that no attempts were made to conduct studies with radiolabeled -$S^{14}CH_3$ or tract methyl mercaptan formation using non-radiolabeled methods. Aventis states that, given the ubiquitous nature of the compound, the low concentrations that could be formed from fenamidone would be much lower than those formed by other organisms.

7. Although the concentration of fenamidone decreased slightly in the pH 9 buffer solution during frozen storage, this decrease is not expected to affect the interpretation of the study since the quantitative data were from samples that were analyzed shortly after collection. Stored samples were used primarily for LC/MS analysis.

8. In the summary table presented on p. 41 (Table XIII), the study author does not report the concentrations for all transformation products at all sampling intervals. Compounds that did not show a pattern of formation or decline but are detected only occasionally at concentrations generally <1% of the applied are not included.

V. REFERENCES:

1. EPA: 40 CFR 158 Subdivision N; Environmental Fate Pesticide Assessment Guideline: §161-1.

2. E.C. C7: Dégradation abiotique - Hydrolyse en fonction du pH. Journal officiel des Communautés européennes, N° L 383 A/229, 29/12/92.

3. RPA407213 active ingredient - Water solvent solubility. A. Certon, J. Cousin and G. Turner. Rhône-Poulenc Agro Report - R&D/CRLD/AN/9715441, 1997 (Study no. 96-79).

Attachment 1

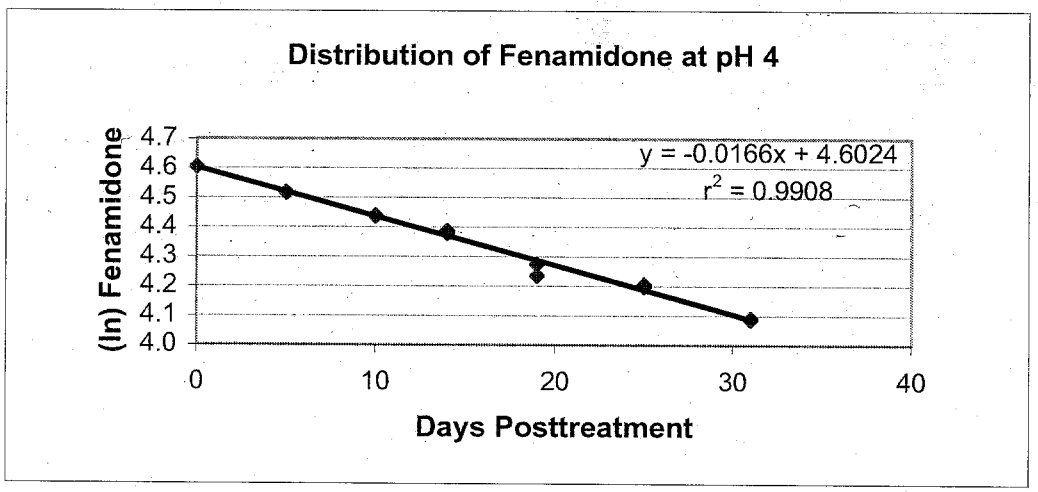
Excel Worksheets

Chemical Name	Fenamidone
PC Code	46679
MRID	45385829
Guideline No.	161-1

pH 4

Half-life:	41.8 Days

Day	% of Fenamidone	ln (% parent)
0	100.0	4.6052
0	100.0	4.6052
5	91.7	4.5186
5	91.5	4.5166
10	84.7	4.4389
10	84.5	4.4370
14	79.7	4.3785
14	80.4	4.3869
19	69.1	4.2350
19	71.8	4.2740
25	67.1	4.2057
25	66.5	4.1978
31	59.8	4.0912
31	59.5	4.0863

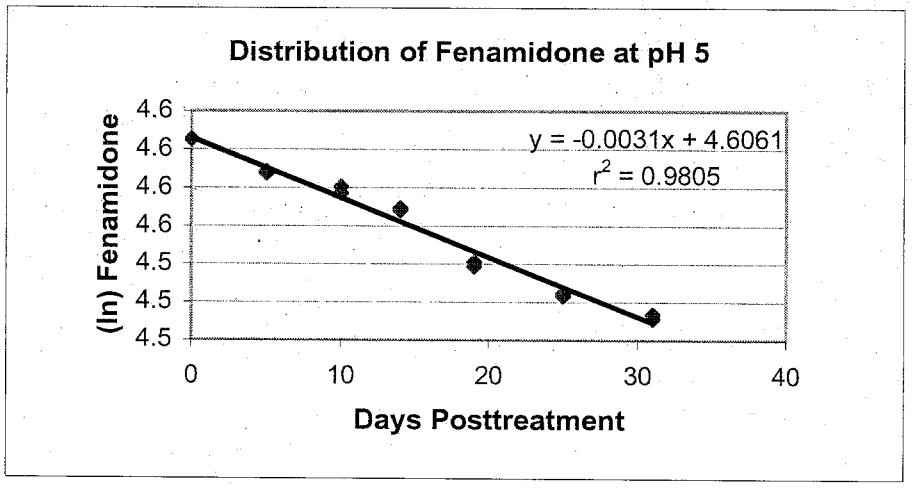


Chemical Name	Fenamidone
PC Code	46679
MRID	45385829
Guideline No.	161-1

pH 5

Half-life:	223.6 Days

Day	% of Fenamidone	ln (% parent)
0	100.0	4.6052
0	100.0	4.6052
5	98.3	4.5884
5	98.3	4.5875
10	97.6	4.5805
10	97.2	4.5771
14	96.4	4.5682
14	96.5	4.5693
19	93.8	4.5411
19	93.6	4.5389
25	92.3	4.5248
25	92.2	4.5234
31	91.3	4.5136
31	91.0	4.5113

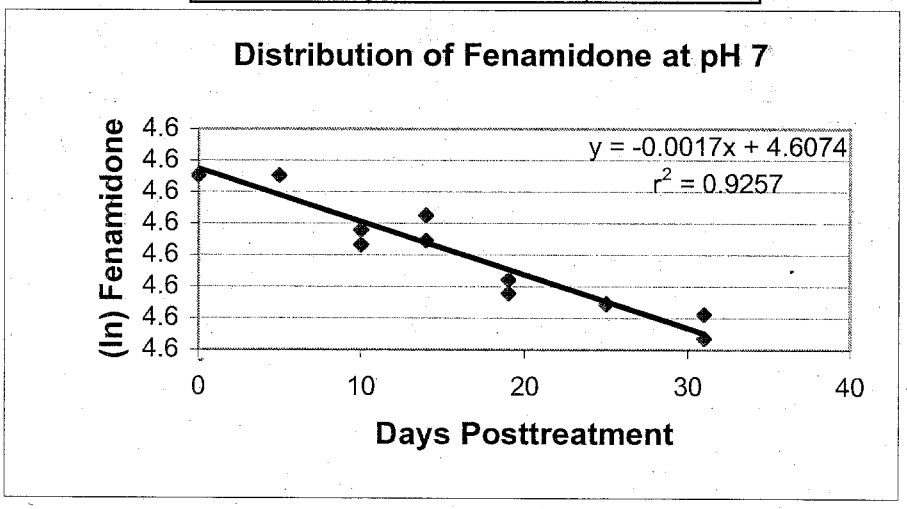


Chemical Name Fenamidone
PC Code 46679
MRID 45385829
Guideline No. 161-1

pH 7

Half-life:	407.7 Days

Days	% of Fenamidone	ln (% parent)
0	100	4.6052
0	100	4.6052
5	100	4.6052
5	100	4.6052
10	98.29	4.5879
10	97.83	4.5832
14	98.74	4.5925
14	97.96	4.5846
19	96.75	4.5721
19	96.34	4.5679
25	96.01	4.5645
25	96.03	4.5647
31	95.7	4.5612
31	94.98	4.5537

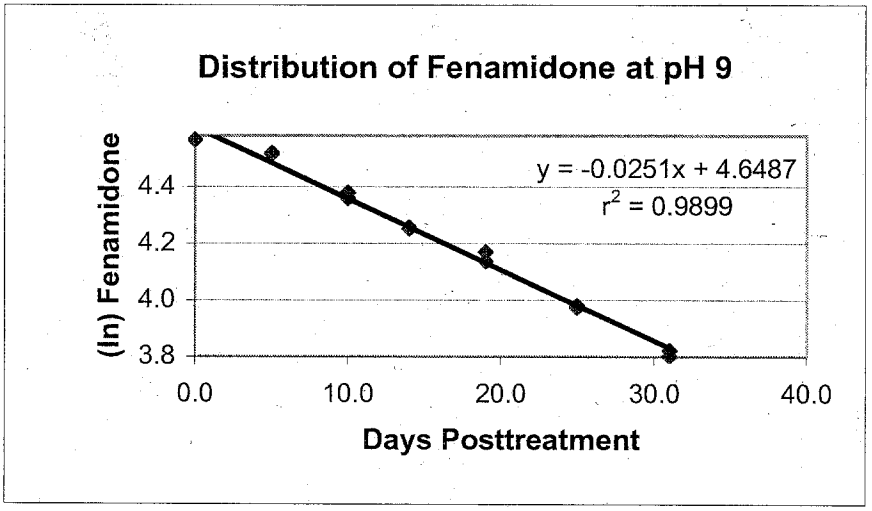


Chemical Name	Fenamidone
PC Code	46679
MRID	45385829
Guideline No.	161-1

pH 9

Half-life:	27.6 Days

Days	% of Fenamidone	ln (% parent)
0	100.0	4.605170186
0	100.0	4.605170186
5	95.6	4.559858963
5	95.2	4.556295018
10	83.1	4.419683626
10	81.4	4.399252415
14	73.5	4.29701326
14	73.2	4.292512127
19	67.5	4.211386583
19	65.2	4.176845784
25	55.4	4.014218518
25	55.8	4.02087741
31	47.6	3.86220231
31	46.6	3.842244111



Chemical name: Fenamidone
Study ID: MRID 45385829
161-1

Table 4

Days	Fenamidone	Hydrolate A	Hydrolate B	Hydrolate C	Hydrolate D	Others	Recovery
0	100	0	0	0	0	0	101.5456
0	100	0	0	0	0	0	100.7905
average	100	0	0	0	0	0	101.1681
s.d.	0	0	0	0	0	0	0.533939
5	91.71	8.3	0	0	0	0	101.5475
5	91.52	8.48	0	0	0	0	101.6016
average	91.615	8.39	0	0	0	0	101.5745
s.d.	0.134350288	0.127279221	0	0	0	0	0.038233
10	84.68	15.32	0	0	0	0	100.2778
10	84.52	15.48	0	0	0	0	103.4418
average	84.6	15.4	0	0	0	0	101.8598
s.d.	0.113137085	0.113137085	0	0	0	0	2.237271
14	79.72	20.28	0	0	0	0	102.0397
14	80.39	19.61	0	0	0	0	99.79864
average	80.055	19.945	0	0	0	0	100.9192
s.d.	0.473761543	0.473761543	0	0	0	0	1.584679
19	69.06	24.95	0.75	0	0	5.26	100.4792
19	71.81	26.32	0.48	0	0.98	0.42	100.1473
average	70.435	25.635	0.615	0	0.49	2.84	100.3132
s.d.	1.944543648	0.96873629	0.190918831	0	0.692964646	3.422397	0.23467
25	67.07	32.93	0	0	0	0	102.4741
25	66.54	33.46	0	0	0	0	102.1087
average	66.805	33.195	0	0	0	0	102.2914
s.d.	0.374766594	0.374766594	0	0	0	0	0.2584
31	59.81	38.71	0.38	0.29	0.46	0.36	99.53948
31	59.52	38.82	0	0	1.28	0.39	99.4127
average	59.665	38.765	0.19	0.145	0.87	0.375	99.47609
s.d.	0.205060967	0.077781746	0.268700577	0.205060967	0.579827561	0.021213	0.089649

Chemical Name: Fenamidone
Study ID: MRID 45385829
161-1

Table 5

Days	Fenamidone	Hydrolate A	Hydrolate B	Hydrolate C	Hydrolate D	Others	Recovery
0	100	0	0	0	0	0	100.069
0	100	0	0	0	0	0	97.29281
average	100	0	0	0	0	0	98.6809
s.d	0	0	0	0	0	0	1.96305
5	98.34	1.66	0	0	0	0	99.42202
5	98.25	1.76	0	0	0	0	100.4698
average	98.295	1.71	0	0	0	0	99.94593
s.d	0.06363961	0.070710678	0	0	0	0	0.740923
10	97.56	2.45	0	0	0	0	100.0373
10	97.23	2.78	0	0	0	0	97.77757
average	97.395	2.615	0	0	0	0	98.90743
s.d	0.233345238	0.233345238	0	0	0	0	1.597862
14	96.37	3.63	0	0	0	0	101.5997
14	96.48	3.15	0	0	0.38	0	99.15727
average	96.425	3.39	0	0	0.19	0	100.3785
s.d	0.077781746	0.339411255	0	0	0.268700577	0	1.727062
19	93.79	4.31	0.74	0	0.87	0.31	101.637
19	93.59	4.49	0.82	0	0.82	0.3	100.8632
average	93.69	4.4	0.78	0	0.845	0.305	101.2501
s.d	0.141421356	0.127279221	0.056568542	0	0.035355339	0.007071	0.547123
25	92.28	5.68	0.7	0	0.79	0.56	100.6376
25	92.15	5.62	0.96	0.34	0.62	0.33	101.4412
average	92.215	5.65	0.83	0.17	0.705	0.445	101.0394
s.d	0.091923882	0.042426407	0.183847763	0.240416306	0.120208153	0.162635	0.568217
31	91.25	6.89	1.16	0	0	0.22	98.48979
31	91.04	6.85	1.13	0	0.99	0	98.33691
average	91.145	6.87	1.145	0	0.495	0.11	98.41335
s.d	0.148492424	0.028284271	0.021213203	0	0.700035713	0.155563	0.108106

Chemical Name: Fenamidone
Study ID: MRID 45385829
161-1

Table 6

Days	Fenamidone	Hydrolate A	Hydrolate B	Hydrolate C	Hydrolate D	Others	Recovery
0	100	0	0	0	0	0	98.52522
0	100	0	0	0	0	0	98.52522
average	100	0	0	0	0	0	98.52522
s.d.	0	0	0	0	0	0	0
5	100	0	0	0	0	0	98.82539
5	100	0	0	0	0	0	99.67931
average	100	0	0	0	0	0	99.25235
s.d.	0	0	0	0	0	0	0.603813
10	98.29	0	1.09	0.63	0	0	101.9987
10	97.83	0.22	1.15	0.81	0	0	98.67064
average	98.06	0.11	1.12	0.72	0	0	100.3347
s.d.	0.325269119	0.155563492	0.042426407	0.127279221	0	0	2.353287
14	98.74	0	1.27	0	0	0	99.65321
14	97.96	0	1.25	0	0.8	0	98.58115
average	98.35	0	1.26	0	0.4	0	99.11718
s.d.	0.551543289	0	0.014142136	0	0.565685425	0	0.758062
19	96.75	0.34	2.05	0	0.88	0	98.52149
19	96.34	0.56	2.16	0	0.95	0	97.19586
average	96.545	0.45	2.105	0	0.915	0	97.85867
s.d.	0.28991378	0.155563492	0.077781746	0	0.049497475	0	0.93736
25	96.01	0.4	2.59	0	0.91	0.11	101.3405
25	96.03	0.64	2.42	0	0.92	0	101.4748
average	96.02	0.52	2.505	0	0.915	0.055	101.4077
s.d.	0.014142135	0.169705627	0.120208153	0	0.007071068	0.077782	0.094923
31	95.7	0.64	2.92	0	0.75	0	93.64221
31	94.98	0.98	2.84	0	1.21	0	98.69861
average	95.34	0.81	2.88	0	0.98	0	96.17041
s.d.	0.509116882	0.240416306	0.056568542	0	0.325269119	0	3.575415

Chemical Name: Fenamidone
Study ID: MRID 45385829
161-1

Table 7

Days	Fenamidone	Hydrolate A	Hydrolate B	Hydrolate C	Hydrolate D	Hyrdolate E	Others	Recovery
0	100	0	0	0	0	0	0	100.4624
0	100	0	0	0	0	0	0	101.3182
average	100	0	0	0	0	0	0	100.8903
s.d	0	0	0	0	0	0	0	0.605131
5	95.57	0	4.44	0	0	0	0	102.4984
5	95.23	0	4.78	0	0	0	0	100.9938
average	95.4	0	4.61	0	0	0	0	101.7461
s.d	0.240416306	0	0.240416306	0	0	0	0	1.063923
10	83.07	1	12.12	0.94	2.88	0	0	100.7383
10	81.39	1.38	12.03	1.51	3.71	0	0	99.65508
average	82.23	1.19	12.075	1.225	3.295	0	0	100.1967
s.d	1.187939392	0.268700577	0.06363961	0.403050865	0.586898628	0	0	0.765972
14	73.48	1.91	17.04	1.07	4.55	0.92	1.05	100.4456
14	73.15	1.52	17.75	1.07	4.63	0.48	1.41	100.6246
average	73.315	1.715	17.395	1.07	4.59	0.7	1.23	100.5351
s.d	0.233345238	0.275771645	0.502045815	0	0.056568542	0.311126984	0.254558	0.126563
19	67.45	1.85	23.5	0	5.77	1.44	0	99.52643
19	65.16	2.52	24.35	0	5.98	1.07	0.94	99.34558
average	66.305	2.185	23.925	0	5.875	1.255	0.47	99.436
s.d	1.619274529	0.473761543	0.601040764	0	0.148492424	0.261629509	0.66468	0.127882
25	55.38	3.1	29.33	1.37	7.09	2.86	0.88	101.6202
25	55.75	3.12	27.63	0.4	8.65	3.91	0.56	100.7048
average	55.565	3.11	28.48	0.885	7.87	3.385	0.72	101.1625
s.d	0.261629509	0.014142136	1.202081528	0.685893578	1.103086579	0.74246212	0.226274	0.647319
31	47.57	3.89	32.33	0	10.19	4.37	1.67	100.3766
31	46.63	3.63	32	0.44	9.98	4.77	2.57	100.8073
average	47.1	3.76	32.165	0.22	10.085	4.57	2.12	100.592
s.d	0.664680374	0.183847763	0.233345238	0.311126984	0.148492424	0.282842712	0.636396	0.304543

Attachment 2

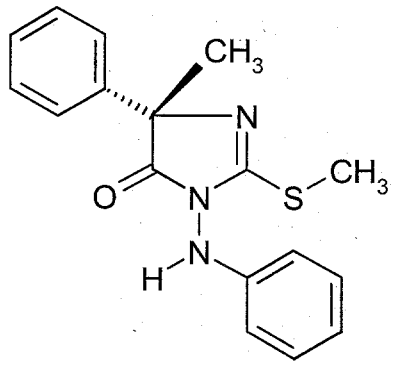
Structures of Parent and Transformation Products

RPA 407213

IUPAC name: (*S*)-5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (S)-

CAS #: 161326-34-7

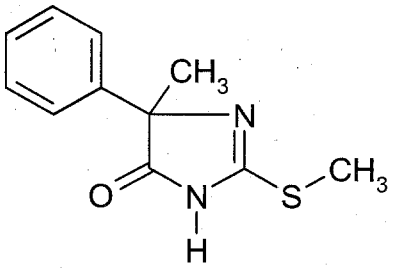


RPA 408056

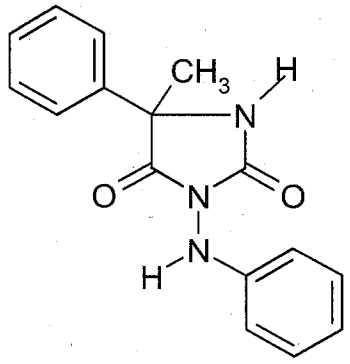
IUPAC name: 5-Methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one

CAS name: 4*H*-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-

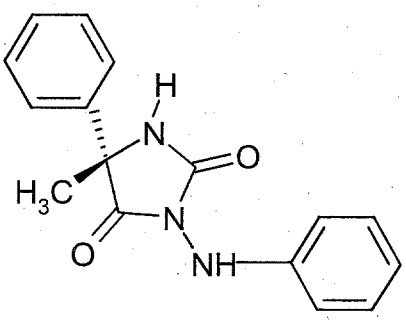
CAS #: N/A



RPA 405862
IUPAC name: 5-Methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione
CAS name: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-3-(phenylamino)-
CAS #: 153969-11-0



RPA 410193
IUPAC name: (S)-4-Methyl-4-phenyl-1-phenylaminoimidazolidin-2,5-dione
CAS name: N/A
CAS #: N/A

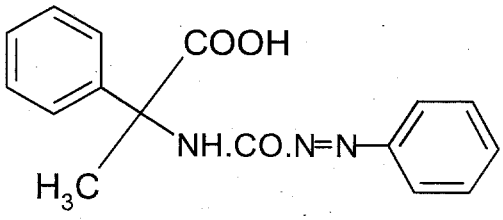


RPA 409344

IUPAC name: (R,S)-2-methyl-2-phenyl-N-(phenylazocarbonyl)glycine
(R,S)-2-phenyl-2-(phenylazocarbonylamino)propionic acid

CAS name: N/A

CAS #: N/A



Attachment 3

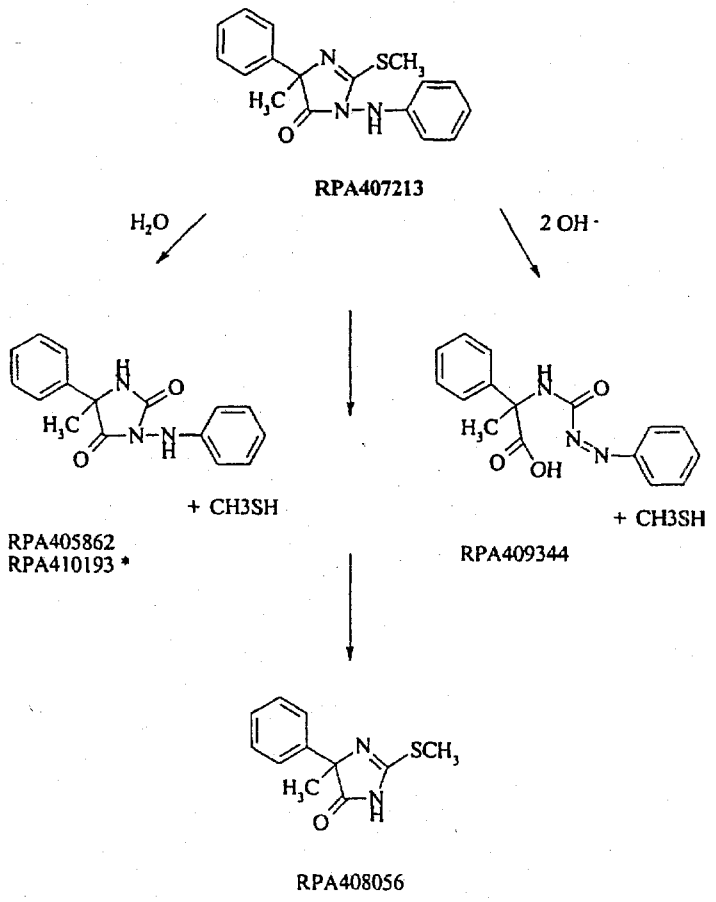
Transformation Pathway Presented by Registrant

4.5.3. Graphical representations

The logarithmic representation of RPA407213 versus time for all the pH is shown in Figure1. The linear representations of RPA407213 and its degradates versus time for each pH are shown in Figures 2 to 5.

5. Conclusion - Hydrolytic pathway of RPA407213

RPA407213 is rather stable in aqueous solutions buffered at pH 5 and 7.
It is hydrolyzed in aqueous solutions buffered at pH 4 and 9: at pH 4, the main degradate is RPA405862/RPA410193; at pH 9, the main one is RPA409344, followed by RPA 408056.
The hydrolytic pathway proposed is as follows :



On the left: the main route of degradation in acidic solution
On the right: the main route of degradation in basic solution

*: RPA410193 is the enantiomeric form, corresponding to RPA407213, of the racemic RPA405862